Remarks

Claims 1-5 and 30 are pending. Claims 1-5 have been amended to clarify the claim language and to remove non-elected sequences from the claims.

Withdrawn claims 8, 9, 16, 21, 22, 25-27, 29 and 31 have been canceled without prejudice to pursuing such claims in a continuing application.

New claims 32-39 have been added. These claims are analogous to (withdrawn and now canceled) claims 8, 21, 22, 25-27, 29 and 31, but based on the combination of primers and probe for detection of HPV type 18, these being a NASBA P1 primer comprising SEQ ID No:20 and a NASBA P2 primer comprising SEQ ID NO:16.

Support for the claim amendments is found in the claims as filed and throughout the specification. No new matter has been added.

Election/Restriction

The Examiner indicate that a complete reply to the final rejection must include cancellation of nonelected claims. Applicant notes that the instant Office action is not a final rejection of the claims (see summary page and p. 2, ¶1), and therefore the requirement to cancel nonelected claims is improper. Applicant respectfully requests reconsideration

Claim Objections

The Examiner objected to claims 1-5 and 30 as reciting nonelected sequences. Applicant has amended the claims to remove any recitation of nonelected sequences, and accordingly respectfully requests that the objection to the claims be withdrawn.

Rejection Under 35 U.S.C. § 102

1. The Examiner rejected claims 1 and 2 under 35 U.S.C. § 102(b) as anticipated by Von Knebel-Doberitz (US 6,027,891). Applicant respectfully traverses the rejection.

SEQ ID NOs:4 and 21 of Von Knebel-Doberitz include sequences that are complementary to SEQ ID NO:20. As discussed previously, Applicant does not consider that disclosure of an oligonucleotide comprising a complementary sequence should be prejudicial to novelty of claims 1 and 2, which claim synthetic or isolated oligonucleotides. The nucleotide sequences of Von Knebel-Doberitz and the claimed oligonucleotides of Applicant are not the same due to the aforementioned complementarity.

The Examiner acknowledges the difference in the sequences, but asserts that in teaching a complementary sequence, Von Knebel-Doberitz inherently teaches the complement. This is not correct because, as noted by the Examiner on p. 3, ¶5, the sequences taught be Von Knebel-Doberitz are oligonucleotide primers used for PCR. Oligonucleotide primers are not inherently double stranded, and in fact as used in the Von Knebel-Doberitz reference for PCR amplification, must be single stranded. Therefore, there is no inherent disclosure of double stranded or complementary nucleic acid molecules and thus no disclosure of Applicant's claimed sequences.

Reconsideration of this rejection is respectfully requested.

2. The Examiner rejected claims 1 and 2 under 35 U.S.C. § 102(e) as anticipated by Anthony (US 2004/0214302 A1).

The Examiner alleges that the claims are anticipated because Anthony provides SEQ ID NO:95, which is alleged to contain the exact sequence of SEQ ID NO:20 of the instant application, with additional 5' and 3' sequences.

Applicant has amended the claims to recite that the claimed oligonucleotide comprises a NASBA P1 primer. As is clearly stated in the specification (see, e.g., paragraphs [0005] and [0012] of the published application), the designation of an oligonucleotides as a "NASBA P1 primer" requires the presence of a promoter functionality at the 5' end of the primer. Applicant asserts that SEQ ID NO:95 of Anthony does not have the required promoter functionality of a NASBA P1 primer.

Accordingly, reconsideration of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

1. The Examiner rejected claims 1, 2 and 4 under 35 U.S.C. § 103 over Shimada in view of Buck and further in view of Simpkins. Applicant respectfully traverses the rejection.

The Examiner asserts that Shimada discloses sequence 18-3, which is alleged to correspond to SEQ ID NO:16 of the instant application, except that it is lacking two 3' nucleotides present in SEQ ID NO:16. Shimada does not teach Applicant's SEQ ID NO:16 or suggest which nucleotides should be added to sequence 18-3 to arrive at Applicant's sequence.

SEQ ID NO:16 is intended for use as a NASBA P2 primer for amplification of HPV mRNA, whereas Shimada is entirely concerned with a diagnostic method based on PCR amplification of HPV DNA, which simply would not make use of a NASBA P2 primer. To reflect this difference claim 1 was amended to require the presence of sequence GATGCAAGGTCGCATATGAG at the 5' end of the primer comprising SEQ ID NO:16. A skilled person would not be motivated to modify p18-3 of Shimada by inclusion of this sequence to produce a NASBA P2 primer, since Shimada's method is entirely based on amplification of HPV DNA not mRNA. Simpkins teaches the inclusion of this sequence in NASBA P2 primers, but only for amplification of mRNA target molecules. Applicant maintains that Buck is not of

relevance to the selection of NASBA primers because Buck is concerned with selection of primers for DNA sequencing, which is not relevant to the selection of NASBA primers.

Thus Shimada does not teach or suggest Applicant's sequences, nor do the secondary references provide the teaching that is lacking in Shimada. Therefore the combination of Shimada and the secondary references does not make out a *prima facie* case of obviousness.

Moreover, contrary to the Examiner's assertions, there is no motivation for one of ordinary skill in the art to specifically modify the sequences of Shimada to obtain Applicant's claimed sequences. The Examiner has not shown where in the Shimada (or elsewhere) there is any suggestion to modify the sequences of Shimada to create structurally distinct chemical compounds as are now claimed.

Instead, the Examiner states that (1) the sequence difference appears to be a user preference and (2) since Buck demonstrated primer equivalence, the skilled person would have a reasonable expectation of success. Applicant respectfully disagrees. First, the differences in sequence are not merely a user preference, but even if so, some motivation to modify Shimada's sequences must be demonstrated by the Examiner. This has not been done. Second, Buck demonstrated primer equivalence, if at all, for DNA sequencing primers. Buck did not demonstrate equivalence for amplification primers, more specifically for PCR primers for amplifying DNA (Shimada) versus NASBA primers for amplifying mRNA (Applicant). Therefore, the requisite motivation and expectation of success has not been demonstrated as required for a *prima facie* case of obviousness.

Simpkins does not provide the elements missing from the Shimada or Buck references, nor the motivation or expectation of success in modifying these references.

Therefore, the combination of references does not render obvious the claimed invention.

2. The Examiner rejected claims 1, 5 and 30 under 35 U.S.C. § 103 over Shimada in view of Tyagi (Nat. Biotech. 14:303-308, 1996) and further in view of Buck. Applicant respectfully traverses the rejection.

The Examiner asserts that Shimada discloses sequence p818 II, which is alleged to correspond to SEQ ID NO:18 of the instant application, except that there are several differences between the two sequences. More specifically, two of the nucleotides of p818 II do not match SEQ ID NO:18, three 3' nucleotides of SEQ ID NO:18 are not present, and two 5' nucleotides that are not present in SEQ ID NO:18 are present in p818 II. These are not "minor differences" as asserted by the Examiner on p. 10 of the Office Action. Shimada does not teach or suggest which nucleotides should be changed, added or removed in sequence p818 II to arrive at Applicant's sequence.

The assertion that it would have been obvious to modify the p818 II sequence of Shimada to prepare SEQ ID NO:18 of Applicant by adding and substituting 7 specific nucleotides appears to be entirely a function of hindsight. The Examiner relies on Buck as providing for "equivalence" of primers. However, Buck apparently reported the use of primers that corresponded exactly to the particular sequence. Buck did not report modifying primer sequences as is asserted by the Examiner to be obvious. Moreover, as noted above, Buck relates to DNA sequencing primers, which differs significantly from NASBA primers. Given the limited teachings of Buck, that the skilled person would not view Buck's teaching as providing either motivation or a reasonable expectation of success with respect to making drastic changes to the nucleotide sequence of Shimada, without guidance as to which specific changes to make, and providing the specific function demonstrated by Applicant. The only way to arrive at Applicant's sequence from Shimada's sequences is through an improper application of hindsight.

Tyagi does not provide the elements missing from the Shimada or Buck references; nor the motivation or expectation of success in modifying these references.

Therefore, the combination of references does not render obvious the claimed invention. Accordingly, Applicant respectfully requests withdrawal of this rejection.

3. The Examiner rejected claims 2 and 3 under 35 U.S.C. § 103 over Von Knebel-Doberitz in view of Kievits and further in view of Yates. Applicant respectfully traverses the rejection.

As argued above in response to an anticipation rejection, SEQ ID NOs: 4 and 21 of Von Knebel-Doberitz contain sequences complementary to SEQ ID NO:20, but Von Knebel-Doberitz does not teach, explicitly or inherently, Applicant's sequence. Nor would a skilled reader be motivated to use a primer comprising a sequence complementary to SEQ ID NO 4 or 21 of Von Knebel-Doberitz for the purposes of amplifying HPV mRNA for the following reasons.

The method of Von Knebel-Doberitz is dependent on the use of a 5' primer which is specific for a portion of the HPV E6-E7 mRNA and a common 3' primer (also referred to as a 3' RACE primer) which is not specific for HPV. Von Knebel-Doberitz teaches that it is essential perform the first amplification (step (c) in the claimed method) using the common 3' RACE primer in order to amplify the extreme 3' end of the transcript. A primer comprising Applicant's SEQ ID NO:20 is not suitable for use in this method since it cannot be used in combination with a 3' RACE primer to amplify a portion of the HPV transcript. The primer embodying SEQ ID NO:20 would anneal to the same strand as the 3' RACE primer. In fact, use of SEQ ID NO:20 (in combination with a suitable forward primer) results in amplification of a completely different portion of the E6-E7 mRNA, upstream of that amplified in the method of Von Knebel-Doberitz.

The Examiner has seemingly rejected this argument because the invention is not directed to a method of amplifying a specific region of the E6 gene, but rather a specific primer molecule comprising a portion of E6 and a T7 promoter region. The Examiner further states that the "ordinary practitioner would have recognized that this region of the E6 gene could be targeted using a forward primer, as taught by Von Knebel-Doberitz, or a reverse primer (based on the complementary sequence)". Office Action at page 20.

Applicant strongly disagrees with the Examiner's reasoning on this point. Any person skilled in the art of molecular biology knows that primers are inherently directional molecules

and that primers which are complementary to each other are not functionally equivalent or functionally interchangeable since they prime synthesis of different nucleic acid strands. As such, complementary primers must be viewed as "targeting" different regions of the E6 gene.

In the context of nucleic acid amplification by PCR (as taught by Von Knebel-Doberitz) primers do not work in isolation; they are designed to work in pairs in order to "target" a particular region of a nucleic acid molecule. The forward primer of Von Knebel-Doberitz is designed to work in combination with the 3' RACE primer in order to "target" a particular region of the target transcript which includes all the regions 3' of the E7 ORF. Targeting of the 3' end of the transcript is essential to the method of Von Knebel-Doberitz. A primer complementary to SEQ ID NOs:4 or 21 of Von Knebel-Doberitz would clearly not allow targeting of the same region of the transcript. Applicant therefore asserts that the skilled person would not be motivated to produce a primer which manifestly would not work in the method described.

Therefore, the combination of references does not render obvious the claimed invention. Accordingly, Applicant respectfully requests that the Examiner withdraw this rejection.

4. The Examiner rejected claims 1, 5 and 30 under 35 U.S.C. § 103 over Cummins or Hendricks in view of Tyagi. Applicant respectfully traverses the rejection.

SEQ ID NO:36 of Cummins, which includes SEQ ID NO:18 of the present application, is described as a primer useful in amplification of human papillomavirus genomic DNA. Neither Cummins nor Tyagi provides any reason why one would choose to modify this particular sequence, out of the many oligonucleotide sequences disclosed by Cummins, to form a molecular beacon probe. Modification of SEQ ID NO:36 of Cummins to form a molecular beacon probe as taught by Tyagi would prevent function as a primer, since the molecular beacon molecules taught by Tyagi lack the free 3' hydroxyl group required for function as a primer (due to attachment of the quencher DABCYL). Hence the modified molecule would no longer be suitable for its intended use in the method of Cummins.

In addition, Cummins already describes a number of oligonucleotide molecules which are suitable for use as probes in the detection of HPV DNA. SEQ ID NO:36 is not described as being useful as a probe. As such, the skilled person faced with the teaching of Cummins would have selected one of the sequences already described as being useful as probes to form the basis of a molecular beacon, not one of the primers. There is no motivation provided for the skilled person to do anything else.

Probe 18-4 of Hendricks comprises the complement of SEQ ID NO:18, plus an additional 17 nucleotides at the 5' end. If one skilled in the art were to modify probe 18-4 to produce a molecular beacon probe (for which Applicant does not concede any motivation or expectation of success), the result would be a molecular beacon comprising complementary sequence to SEQ ID NO:18. Hendricks provides no motivation for one skilled in the art to produce a probe of complementary sequence to probe 18-4. In fact, Hendricks teaches that it is essential for probe 18-4 (and the other probes specifically described) to be complementary to the E6 and/or E7 ORF such that it is capable of hybridizing to E6/E7 mRNA as well as to sense strands of HPV genomic DNA. It can be clearly seen in Figure 2 that all of the probes used in the method of Hendricks hybridise to the sense strand (i.e. strands of mRNA).

Furthermore, the Examiner's assertion that a teaching of a sequence is an inherent teaching of the complement of the sequence is without foundation. As for the argument presented above against anticipation by Von Knebel-Doberitz, oligonucleotide primers are not inherently double stranded, and in fact as used in Hendricks, are taught to be single stranded. Therefore, there is no inherent disclosure of double stranded or complementary nucleic acid molecules and thus no disclosure of Applicant's claimed sequences.

Tyagi does not provide the elements missing from the Cummins or Hendricks methods, nor the motivation or expectation of success in modifying these references.

Therefore, the combination of references does not render obvious the claimed invention. Accordingly, Applicant respectfully requests that the Examiner withdraw this rejection.

Double Patenting Rejection

The Examiner provisionally rejected claims 1-5 and 30 under the judicially-created doctrine of obviousness-type double patenting over claims 10 and 12 of copending application serial number 10/500832.

As noted by the Examiner in making this a provisional rejection, the claims of the cited application have not yet been allowed. Therefore, Applicant believes that it is premature to address the rejection, and respectfully requests reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the foregoing amendments and remarks, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
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Docket No. B0192.70052US00
Date: January 18, 2007
X01/18/07X